

## STUDY PROTOCOL

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# Use of dexmedetomidine for prophylactic analgesia and sedation in delayed extubation patients after craniotomy: a study protocol and statistical analysis plan for a randomized controlled trial

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## Abstract

**Background:** Pain and agitation are common in patients after craniotomy. They can result in tachycardia, hypertension, immunosuppression, increased catecholamine production and increased oxygen consumption. Dexmedetomidine, an alpha-2 agonist, provides adequate sedation without respiratory depression, while facilitating frequent neurological evaluation.

**Methods/design:** The study is a prospective, randomized, double-blind, controlled, parallel-group design. Consecutive patients are randomly assigned to one of the two treatment study groups, labeled 'Dex group' or 'Saline group.' Dexmedetomidine group patients receive a continuous infusion of 0.6 µg/kg/h (10 µg/ml). Placebo group patients receive a maintenance infusion of 0.9% sodium chloride for injection at a volume and rate equal to that of dexmedetomidine. The mean percentages of time in optimal sedation, vital signs, various and adverse events, the percentage of patients requiring propofol for rescue to achieve/maintain targeted sedation (Sedation-Agitation Scale, SAS 3 to 4) and total dose of propofol required throughout the study drug infusion are collected. The percentage of patients requiring fentanyl for additional rescue to analgesia and total dose of fentanyl required are recorded. The effects of dexmedetomidine on hemodynamic and recovery responses during extubation are measured. Intensive care unit and hospital length of stay also are collected. Plasma levels of epinephrine, norepinephrine, dopamine, cortisol, neuron-specific enolase and S100-B are measured before infusion (T1), at two hours (T2), four hours (T3) and eight hours (T4) after infusion and at the end of infusion (T5) in 20 patients in each group.

**Discussion:** The study has been initiated as planned in July 2012. One interim analysis advised continuation of the trial. The study will be completed in July 2013.

**Trial registration:** ClinicalTrials (NCT): ChiCTR-PRC-12002903.

**Keywords:** Dexmedetomidine, Analgesia, Sedation, Prophylactic, Delayed extubation, Craniotomy

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## Background

Pain and agitation are major concerns in postoperative care of neurosurgical patients. Several studies have shown that moderate-to-severe postoperative pain is frequent following craniotomy [1-7]. In a recent study by Mordhorst *et al.* [2], 55% of patients had moderate or severe postoperative pain in the first 24 hours following craniotomy. This study had a similar result to the pilot study by De Benedittis *et al.* [3] in which 60% of patients experienced postoperative pain. Agitation is common in the ICU. It has been found that there are multiple possible causes of agitation in the ICU setting, including the presence of existing diseases, pain, anxiety, delirium, dressing changes, invasive procedures, nursing procedures, intubation, endotracheal tubes and surgical incisions [8,9]. Pain and agitation can cause tachycardia, hypertension, increased catecholamine production, increased oxygen consumption and immunosuppression [9,10]. Increased catecholamines have been shown to contribute to myocardial ischemia, disturbed sleep and catabolism [11]. Hypertension can cause an increase in brain edema or hemorrhage, which may give rise to brain herniation [12].

On the other hand, despite a greater awareness of pain and agitation after craniotomy, clinicians remain reluctant to administer analgesics and sedatives in patients following craniotomy. The major concerns are the side effects of these drugs, mainly that they reduce the clinician's ability to monitor the level of consciousness and that they induce respiratory depression [13].

Sedation goals for neurosurgical ICU patients are to improve comfort, overcome anxiety and pain, facilitate nursing care and mechanical ventilation, facilitate frequent neurological assessments and provide sedation without causing deleterious changes in intracranial pressure (ICP) or cerebral perfusion pressure (CPP). An ideal sedative agent in the ICU should be cheap, rapid in onset and offset and without local and systemic adverse effects. There is no sedative agent in use that has all these ideal properties. However, dexmedetomidine, an alpha-2 agonist, provides adequate sedation without respiratory depression, while facilitating frequent neurological evaluation.

Dexmedetomidine, a potent and highly selective alpha-2-adrenoceptor agonist, has been available in the United States since the end of 1999 for use in humans as a short-term (<24 hours) medication for sedation/analgesia in the ICU in initially intubated and mechanically ventilated patients [14].

Dexmedetomidine provides dose-dependent sedation, anxiolysis and analgesia (involving spinal and supraspinal sites) without respiratory depression [15]. Although alpha-2-adrenoceptors are located throughout the body, they are present in larger concentrations in vascular smooth muscle and in key arousal areas of the central nervous system (CNS), such as the locus ceruleus [16]. Activation of

alpha-2-adrenoceptors in the CNS decreases centrally mediated sympathetic activity and induces sedation [16,17]. Activation of presynaptic alpha-2-adrenoceptors in cortical blood vessels decreases norepinephrine release, whereas postsynaptic alpha-2-adrenoceptors may directly increase vascular smooth muscle tone [15-17].

Sedation with dexmedetomidine differs from sedation with other commonly used sedatives such as propofol or midazolam. Dexmedetomidine may induce a sedative state similar to physiologic sleep without respiratory depression by acting on alpha-2 receptors in the locus ceruleus [18-20], and patients may be aroused easily with stimulation and are cooperative once aroused.

In addition to its sedative effects, dexmedetomidine has significant analgesic qualities and may significantly reduce concomitant opioid use. Analgesia with dexmedetomidine is mediated primarily through interaction at alpha-2a within the spinal cord, where drug activity attenuates nociceptive signal transduction. The actual mechanism of action appears to involve an interaction with opioid receptors and, although dexmedetomidine alone has been documented to reduce pain, the effect when given jointly with opioids may be additive or synergistic [21]. Dexmedetomidine provides intense analgesia during the postoperative period and reduces the total number of post-surgical patients requiring opioids with a corresponding reduction in opioid-associated side effects [19].

Dexmedetomidine is accompanied by virtually no respiratory depression at clinically relevant doses. Despite profound sedative properties, dexmedetomidine is associated with only limited respiratory effects, even when dosed to plasma levels up to 15 times those normally achieved during therapy, leading to a wide safety margin [18]. Hypercapnic arousal is preserved, and the apnea threshold is actually decreased. Because dexmedetomidine has no depressant effects on ventilation, its analgesic effect may offer a significant advantage for patients at risk of respiratory decompensation [22].

Hemodynamic effects of dexmedetomidine may result from both peripheral and central mechanisms. Dexmedetomidine is the pharmacologically active dextroisomer of medetomidine [23]. Stimulation of alpha-2 adrenoceptors by dexmedetomidine in pontine locus ceruleus (LC) results in decreased firing of LC neurons secondary to their hyperpolarization. It also has a sympatholytic effect through decreases in the concentration of norepinephrine. This, in turn, decreases the blood pressure (BP) and the heart rate (HR) [24-27]. The initial response to rapid dexmedetomidine infusion may be a transient hypertension. However, the net effect of alpha-2 adrenoceptor action is a significant reduction in circulating catecholamines and a modest decrease in BP and heart rate HR. Although hypotension has been described in patients

receiving dexmedetomidine, this physiological effect seems to correlate with the use of a loading dose and/or pre-existing hypovolemia [15].

A meta-analysis including 24 trials showed that dexmedetomidine did not appear to increase risk of bradycardia. The risk of bradycardia was, however, significantly higher in studies that used both a loading dose and high maintenance doses ( $>0.7$  ug/kg/h) than in studies that did not use both. Risks of hypotension requiring interventions, delirium, self-extubation, myocardial infarction, hyperglycemia, atrial fibrillation and mortality were not significantly different between dexmedetomidine and traditional sedative and analgesic agents [28].

Dexmedetomidine could be a potentially useful anesthetic adjuvant for neurosurgical patients [15]. Two studies have examined its use in patients undergoing intracranial surgery [29,30]. Both studies showed that the addition of dexmedetomidine improves perioperative hemodynamic control. In these studies, the authors controlled arterial blood pressure with a prescribed incremental dosing of anesthetics. No patient in either study required antihypertensive medications. Dexmedetomidine does not have a significant effect on intracranial pressure [15].

Dexmedetomidine also minimizes opioid induced muscle rigidity, decreases post-operative shivering and has hemodynamic stabilizing effects [31]. The medication is a unique sedative in that it does not cause respiratory depression and the sedated patients are easily aroused to perform a neurological examination or to cooperate with procedures (for example, physiotherapy, radiology imaging) without showing irritation [32,33].

Dexmedetomidine has been reported to provide neuroprotective effects against ischemia in the CNS [34-38]. The S100B protein and the neuron-specific enolase (NSE) are the most widely investigated of molecular markers in patients with severe head injury, stroke or subarachnoid hemorrhage (SAH). The concentration of these markers has been shown to increase in the cerebrospinal fluid (CSF) as well as in the serum [39-43]. In addition, in patients with SAH the course of the S100B concentration has been shown to correlate with neurologic deficits and outcome [44,45].

The aim of the present work is to evaluate the safety and efficacy of dexmedetomidine for prophylactic analgesia and sedation in delayed extubation patients after craniotomy. The primary hypothesis is that prophylactic use of dexmedetomidine will increase the percentage of time in optimal sedation.

## Methods/design

The present study is a prospective, single-center, randomized, double-blind, placebo-controlled, two-arm trial in patients with delayed extubation after craniotomy.

## Study setting and population

The study setting is the neurosurgical ICU, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

All patients after intracranial surgery with delayed extubation admitted to our ICU are screened daily for study eligibility. Patients are deemed eligible for this study if they are  $\geq 18$ -years-old, present with motor responses to external stimuli in the Glasgow Coma Scale (GCS-M) equal or higher than five in two hours (time zero would be the time of ICU admission).

Exclusion criteria are:

- Liver insufficiency
- Renal insufficiency
- HR less than 50 bpm
- Systolic BP less than 90 mm Hg
- Acute myocardial infarction
- Second or third degree atrioventricular block
- Need of continuous infusions of vasopressor before the start of study drug infusion
- Consciousness disorders or epilepsy before intracranial surgery
- Pre-existent dysphagia and cough reflex difference
- Emergency operation
- Readmitted to ICU after randomization to the study
- Enrolled in another trial
- Pregnant or lactating women

## Ethical aspects and informed consent

When a patient is identified as eligible for the study, immediate contact will be made with the 24-hour on-call study coordinator, who will confirm eligibility. Delayed extubation patients after craniotomy are often unable to provide consent until they improve. The attending physician will introduce the family to the study coordinator. The physician will make sure the family knows the credentials of the study coordinator, and say that this person is going to discuss a research program that is being conducted, and that this person is qualified to do so. The study coordinator will take the family to a place where they can talk confidentially. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed, to make sure they understand.

The study coordinator will explain that there is a possibility that the patient may experience pain, agitation, and delirium, and, if so, the patient could become worse. The coordinator will say that there is a new alpha-2 agonist that provides adequate sedation without respiratory depression, while facilitating frequent neurological evaluation. He will explain that in a small percentage of patients, dexmedetomidine could cause bradycardia,

hypotension and respiratory depression. The potential advantages of using or not using dexmedetomidine will be described. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study coordinator, local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

A register is kept of all patients evaluated for inclusion and of patients who withdraw from the study. The latter are clinically followed up without their data being analyzed in the study.

The study protocol and consent forms were approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (approval number KY2012-006-02) and by the Chinese Clinical Trial Registry (ChiCTR-PRC-12002903). The Beijing Tiantan Hospitals' Institutional Review Board gave positive advice for the addition of their ICU as the study site.

#### Data collected at study entry

At baseline, data on demographic characteristics and the history of past illnesses of the patients are obtained. The surgical site, operation time, intraoperative medication, the input liquid quantity, and the amount of bleeding and urine are recorded. The Acute Physiology and Chronic Health Evaluation II score (APACHE II) and Glasgow Coma Scale (GCS) are calculated.

#### Randomization, double-blind and allocation concealment

The study has a prospective, randomized, double-blind, controlled, parallel-group design. Consecutive patients are randomly assigned to one of the two treatment study groups, labeled 'Dex group' or 'Saline group.' Randomization is based on a computer generated random digits table and follows a concealed process using sealed and numbered envelopes that allocate the patient to either of the two arms of the study. Patients may be randomized into this study only once unless they were discharged from the hospital and were re-admitted beyond 180 days of the first enrollment. The study does not allow cross-overs and, if any occur, they will be reported as protocol violations.

Experimental drug and placebo with the same character are prepared by a pharmacist. Patients and all study personnel except the investigative pharmacist are blind to treatment assignment. The details of the series are unknown to any of the investigators and are contained in a set of opaque and sealed envelopes, each bearing on the outside only the number.

#### Trial interventions

All patients are randomized 1:1 to receive dexmedetomidine or placebo infusion. Dexmedetomidine group patients receive a continuous infusion of 0.6 µg/kg/h (10 µg/ml). Placebo group patients receive a maintenance infusion of 0.9% sodium chloride for injection at a volume and rate equal to that of dexmedetomidine. The patient's level of sedation will be assessed using the Sedation-Agitation Scale (SAS) per hour after starting the study drug infusion.

Any patient >5 on the SAS will be given rescue propofol in 0.5 mg/kg bolus or infusion doses 0.5 to 2 mg/kg/h until the attaining SAS 3 or 4. Fentanyl will be given in 0.05 mg increments to treat pain as needed.

#### Duration of the intervention

The allocated intervention is continued until any of the following criteria is met:

- A maximum of 24 hours on the study infusion protocol
- 30 minutes after extubation
- ICU discharge

The intervention must be emergency stopped when the following occurs:

- HR <50 bpm after atropine in 0.25 mg bolus
- Systolic BP <90 mmHg after hydroxyethyl starch infusion 250 ml/0.5 h
- Peripheral oxygen saturation (SpO<sub>2</sub>) <90%
- SAS <3

#### Study endpoints

##### The primary endpoints

Our current primary endpoint is the mean percentages of time in optimal sedation (SAS of 3 or 4).

##### Secondary endpoints

The percentage of patients requiring propofol for rescue to achieve/maintain targeted sedation (SAS 3 or 4) and total dose of propofol required throughout the study drug infusion are collected. The percentage of patients requiring fentanyl for additional rescue to analgesia and total dose of fentanyl required are recorded.

Secondary endpoints also include vital signs and various and adverse events. Vital signs are recorded every hour throughout the procedure (BP, HR, respiratory rate (RR), and SpO<sub>2</sub>). Adverse events include hypotension, hypertension, bradycardia, tachycardia, airway obstruction, apnea, epilepsy, cerebral hemorrhage or infarction and consciousness disorders (GCS-M <5).

The effects of dexmedetomidine on hemodynamic and recovery responses during extubation are measured. BP, HR, RR, and SpO<sub>2</sub> are recorded one minute before



extubation, during extubation, and 1, 3, 5, 10 and 30 minutes after extubation. ICU and hospital length of stay (LOS) are also collected.

Plasma levels of epinephrine, norepinephrine, dopamine, cortisol, NSE and S100-B are measured before infusion (T1), two hours (T2), four hours (T3) and eight hours (T4) after infusion and end of infusion (T5) in 20 patients each group.

### Current sample size justification

Primarily, we expect the frequency of the patient's agitation to decrease and a reduction of pain after dexmedetomidine infusion in delayed extubation patients after craniotomy. In our previous studies, the baseline frequency of agitation and pain in delayed extubation patients after craniotomy was 30% and the mean percentage of time in optimal sedation was 88%. It is expected that the mean percentages of time in optimal sedation would increase to 95% after dexmedetomidine infusion. Using the Power and Sample Size Calculation program, we will need to study 72 experimental subjects and 72 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The Type I error probability with testing this null hypothesis is 0.05.

### Statistical analysis

All analyses will be according to the intention-to-treat principle, that is, all randomized patients will be analyzed in the groups to which they were originally allocated and will be blinded to treatment assignment. Baseline characteristics will be summarized by carrying out univariate analyses. Categorical variables will be presented as numbers and percents, percentages, and analyzed by the  $\chi^2$ -test. Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and interquartile range as appropriate. Comparison of continuous variables will be performed using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Plasma levels of epinephrine, norepinephrine, dopamine, cortisol, NSE and S100- $\beta$ , and BP, HR, RR and SpO<sub>2</sub> will be analyzed by repeated measure analysis of variance (ANOVA). All tests of significance will be at the 5% significance level and two-sided. Analyses will be conducted using SPSS 17.0.

### Discussion

A significant difference in the safety and/or efficacy end-points will provide important evidence for optimizing intracranial surgery patient sedation. Also, a neutral result will provide important insight, as this would mean that more studies are needed to evaluate the safety and

efficacy of dexmedetomidine for prophylactic analgesia and sedation in patients after craniotomy.

### Trial status

The study has been initiated as planned in July 2012. One interim analysis advised continuation of the trial. The study will be completed in July 2013.

### Abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation II score; BP: blood pressure; CNS: central nervous system; CPP: cerebral perfusion pressure; CSF: cerebrospinal fluid; GCS: Glasgow Coma Scale; GCS-M: motor responses to external stimuli in GCS; HR: heart rate; ICP: intracranial pressure; LC: locus ceruleus; NSE: neuron-specific enolase; RR: respiratory rate; SAH: subarachnoid hemorrhage; SAS: Sedation-Agitation Scale; SpO<sub>2</sub>: peripheral oxygen saturation.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

LHZ and JXZ participated in the design of the study and drafted the manuscript. ZHS and NNY participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

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